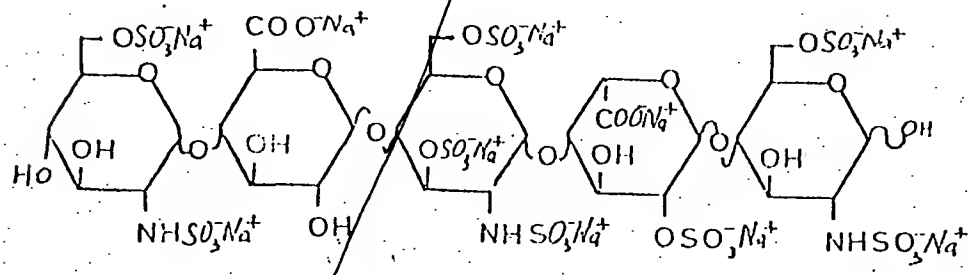
said reaction being carried out in the presence of blocking groups on the other hydroxy groups on the saccharide, which blocking groups are inert in the reaction.

48. The process of claim 42 wherein the oligosaccharide has the formula



(50)

REMARKS

Favorable reconsideration of this application is respectfully solicited.

Applicants note that the Office Action dated January 27, 1984, examined claims 1-4. The Examiner's attention is directed to the fact that a Preliminary Amendment was hand delivered to Group 120 on December 1, 1983, but that the contents of the Preliminary Amendment were not examined in the January 27, 1984 Office Action. A Request for further Office Action re Serial Number 457,931, was hand carried to the Examiner then filed in Group 120 on February 27, 1984. To date no further Office Action has been received. Thus, this Amendment is responsive only to the Examiner's rejection of claims 1-4, and not to a theoretical examination of the added claims 5-41. A copy of the Preliminary Amendment is attached for the convenience of the Examiner.

This invention relates to a process for the synthesis of oligosaccharides which constitute or comprise fragments of acid mucopolysaccharides. The process comprises the reaction of a compound having a glucosamine terminal unit with a compound having a uronic acid terminal unit. In certain cases, the reacting compound consists solely of the glucosamine or uronic acid unit, rather than a chain of two or more saccharides.

Claim 4 is rejected for obviously failing to particularly point out and distinctly claim the invention, as required by 35 USC 112, second paragraph. Claim 4 has been rewritten as claim 48.

Claims 1-3 are rejected under 35 USC 112, second paragraph, as being indefinite in the use of several terms and phrases. Claims 1-3 have been rewritten as claims 42-47. It is believed that the claims as rewritten are now in accordance with proper usage.

Claims 1-3 are rejected under 35 USC 103 as being unpatentable over each of the patents to Szarek et al, Nair et al, Coussediere et al, the PCT French patent or the Kochetkov et al reference.

The Examiner asserts that each of the references discloses the instant conventional process, that the novelty herein is seen to be in the use of other saccharide units, and that the substitution of one saccharide unit for another in the process of the invention is obvious. This rejection is respectfully traversed.

The instant invention relates to a process for the synthesis of acid mucopolysaccharides. The term "acid mucopolysaccharide" refers to compounds which are also called glycosamino glycuronogly-canes (See the specification, page 1, lines 16-18, Lehninger, "Biochemistry", N.Y., P. 272, Exhibit

I). Therefore the synthesis of the instant invention is concerned with the synthesis of compounds having essentially alternating amino sugar units and uronic acid units. The process provides not only for the skeleton of alternating amino sugar and uronic acid morities, but also for functional groups on the chain.

The Coussediere et al patent discloses new derivatives of aminoglycosides and their process of preparation. It does not teach a process which forms a mucopolysaccharide chain of alternating amino sugar and uronic acid units. Additionally, it does not teach a process which requires the use of particular blocking groups on the starting materials of the reaction so that specific substitutions can be made on the trisaccharide chain. Furthermore, the process does not teach the sequential introduction of specific substitution at active sites on the saccharide chain.

The Szarek et al patent discloses the synthesis of L-sucrose or beta-L-fructo-furanosyl-alpha-L-glycopyranoside. The synthesis is based on the reaction of a glycosyl halide with a pentosyl alcohol wherein all of the remaining hydroxy groups are blocked by R. The R groups are then all removed in a single hydrogenation step to produce the desired final compound. The reference does not teach the sequential removal of blocking groups and subsequent introduction of desired specific substitution.

The Nair et al patent discloses galactapyranosyl glucopyranose compounds. There is no teaching of a linkage between an amino sugar to an uronic acid, and there is no teaching of introducing specific substitution, as are found in heparin.

The Sinay et al patent (Fr 7900031), relates to the preparation of antigenic determinants, more particularly of trisaccharide B derivatives. Such an osidic chain comprises a fucopyranose-galactopyranose galactopyranose chain, which is different than the mucopolysaccharide chain of the instant invention. There also is no teaching of introducing specific substitutions, as are found in heparin.

The Kochetkov et al reference relates to the synthesis of antigenic polysaccharides with mannopyranosyl, rhamnopyranosyl and galactopyranosyl units. There is no teaching of alternating amino sugar and uronic acid units; neither is there any teaching of specific substitutions.

The Examiner has stated that to substitute other well known saccharide reactants in the processes, shown by each of the references, is an obvious substitution well within the skill of the art. The Examiner's attention is directed to Paulson, "Advances in Selective Chemical Synthesis of Complex Oligosaccharides", 21 Angewandte Chemie 155 (1982), (Exhibit II), wherein this contention is specifically refuted. The Examiner's attention is specifically directed to page 156, where it is emphasized "that each oligosaccharide synthesis remains an independent problem.... There are no universal reaction conditions for oligosaccharide synthesis". The reference goes on to explain that the reactivies of the two groups involved in the glycosylation reaction are strongly dependent on the blocking patterns of the two compounds, and that a variation of the blocking pattern can exert a decisive influence on the coupling step. Thus, in the instant invention where both amino sugars and uronic acids are involved, the choice of specific reaction conditions and of particular blocking groups is not obvious from previous processes. To provide for the activity

necessary to carry out the glycosylation reaction, while protecting the remaining hydroyl groups in such a manner that they are unaffected by the glysosylation reaction, but can then be sequentially removed and replaced with specific substitutions which are characteristic of heparin, is not obvious from the cited references.

In light of the above remarks, it is believed that the rewritten claims are in the proper condition for allowance and, accordingly, reconsideration is respectfully solicited. Should the Examiner consider that a telephone call to the undersigned would be helpful in the prosecution of this application, she is respectfully invited to call him at the number listed below.

Respectfully submitted,

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Enclosures: Exhibits I, II
Preliminary Amendment

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on June 27, 1984

Signature

6-27-84
Date